PC10866AMGM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Weichao G. Chen, et al.

SERIAL NO.: 09/836,035

FILED: April 17, 2001

FOR: SODIUM-HYDROGEN EXCHANGER TYPE 1 INHIBITOR

Examiner: E. Huang
Art Unit: 1625

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231 on this 16th day of November 2004

By

Assistant Commissioner For Patents
Washington, D.C. 20231

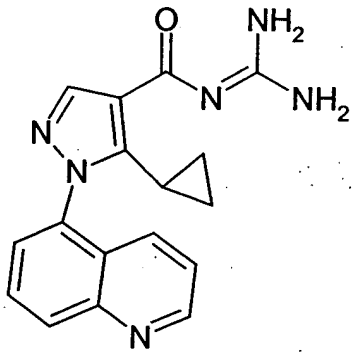
Sir:

37 C.F.R. § 1.132 DECLARATION

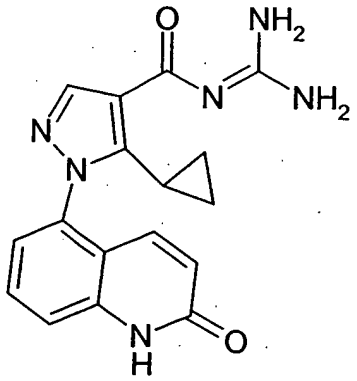
I, Mary C. Allen, a citizen of the United States residing at East Lyme, CT, hereby declare as follows:

1. I obtained a Bachelor of Science degree in Biology in 1986 from Trinity College. In 1995, I earned a Masters of Science degree in Nutritional Biochemistry from the University of Connecticut. From 1986 to present, I have worked at Pfizer Inc where my current position is Senior Scientist.

2. I am familiar with the subject patent application entitled "Sodium-Hydrogen Exchanger Type 1 Inhibitor," filed April 17, 2001 (hereinafter "the instant application"). In particular, I am the pharmacokineticist who conducted plasma half-life analysis on the prior art Hamanaka compound (hereinafter "Compound A") and the instant application Formula I compound (hereinafter "Compound B").



COMPOUND A



COMPOUND B

3. I am familiar with the Office Action, dated July 16, 2001, issued in the instant application. In the Office Action, the Examiner contends that, absent unexpected results, one of ordinary skill in the art would be motivated to arrive at the invention in the instant application from disclosures in the prior art by Hamanaka (WO 99/43663). I am also generally familiar with Hamanaka (WO 99/43663).

4. The utility of Compound B versus Compound A, can be demonstrated by plasma half-life ($t_{1/2}$) measurements. The half-life is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

5. To measure plasma half-life, Compound A was administered as a 24 hour constant intravenous infusion dose to sixteen normal human subjects. Compound B is generated through metabolism via the aldehyde oxidase enzyme. Compound B is measured *in vivo* using an LC/MS/MS bio-analytical assay. A summary of the data is set forth below in Tables 1 and 2.

Table 1. Summary of Mean (SD) Pharmacokinetic Parameters of Compound A Following 24-h Continuous i.v. Infusion of Compound A

Dose (mg/kg/day)	T_{max} (h)	Cavg* (µg/mL)	AUC_{0-t}* (µg·h/mL)	$AUC_{0-\infty}$* (µg·h/mL)	Clp (ml/min/kg)	Vdss (L/kg)	$t_{1/2}$ (h)	% of Dose Excreted in Urine	Clr† (ml/min/kg)
1	5.4 (5.6)	0.04 (0.01)	1.05 (0.20)	1.05 (0.20)	16.0 (2.4)	0.9 (0.4)	2.7 (0.9)	21 (3.9)	3.3 (0.9)
3	4.4 (4.2)	0.11 (0.02)	2.86 (0.67)	2.87 (0.67)	17.7 (3.6)	1.3 (0.7)	3.1 (0.7)	22 (2.2)	4.0 (1.1)
10	9.0 (3.8)	0.44 (0.08)	11.6 (2.39)	11.6 (2.40)	14.6 (3.0)	0.6 (0.3)	5.0 (1.8)	20 (4.2)	2.9 (0.6)
20	16 (9.8)	1.10 (0.14)	27.7 (2.8)	27.7 (2.8)	12.1 (1.8)	1.0 (0.5)	5.7 (0.4)	18 (2.1)	2.2 (0.3)

t = the time of the last quantifiable plasma concentration; Values represent the mean ± SD of 4 subjects/dose.
* means and SD are geometric, all other means and SD are arithmetic.
† Renal clearance of unchanged drug.

Table 2. Summary of Mean (SD) Pharmacokinetic Parameters of Compound B Following 24-h Continuous i.v. Infusion of Compound A

Dose (mg/kg/day)	T_{max}* (h)	C_{max}† (µg/mL)	AUC_{0-t}† (µg·h/mL)	$AUC_{0-\infty}$† (µg·h/mL)	$t_{1/2}$* (h)
1	24 (0)	0.11 (0.037)	2.31 (0.60)	2.40 (0.67)	7.7 (1.7)
3	24.0 (0.04)	0.25 (0.013)	5.90 (0.43)	6.06 (0.45)	7.1 (0.7)
10	24.13 (0.09)	0.74 (0.15)	17.6 (3.27)	18.0 (3.4)	6.8 (0.8)
20	24.04 (0.05)	1.18 (0.14)	30.3 (3.84)	30.9 (3.89)	6.8 (0.4)

t = the time of the last quantifiable plasma concentration; Values represent the mean± SD of 4 subjects/dose.
* arithmetic means and SD
† geometric means and SD

6. Over the dose range tested, 1-20 mg/kg/day, the mean plasma half-life ("$t_{1/2}$") for Compound A was approximately 4 hours compared to $t_{1/2}$ of 7 hours for Compound B. The fact that Compound B has a 3 hour longer $t_{1/2}$ compared to Compound A is important because it may allow for more flexible dosing regimens and provide a longer duration of action, both of which are desirable attributes of this therapeutic agent.

7. Based upon my experience, a person of ordinary skill in the art would not have been able to predict that Compound B would have an almost two-fold improvement in half-life.

8. All statements made herein of my own knowledge are true and all statements made herein on information and belief are believed to be true; and further that these statements are made with the understanding that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C.§ 1001 and that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATED: 11/16/01

Mary C Allen

Mary C. Allen

BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATE PATENT AND TRADEMARK OFFICE

LIMITED RECOGNITION UNDER 37 CFR § 10.9(b)

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This document constitutes proof of such recognition. The original of this document is on file in the Office of Enrollment and Discipline of the U.S. Patent and Trademark Office.

Expires: September 4, 2002

Harry I. Moatz
Director of Enrollment and Discipline